Pulmonary nocardiosis caused by *Nocardia blacklokiae* in an immunocompetent patient

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A B S T R A C T

A subset of *Nocardia* isolates, previously belonging to *N. transvalensis,* has recently been given the new species designation *N. blacklokiae*. Here we report a case of pulmonary nocardiosis caused by *N. blacklokiae* in a 52-year-old immunocompetent woman presenting with low-grade fever and fatigue. The isolated *Nocardia* strain was resistant to sulfamethoxazole-trimethoprim and amikacin, but susceptible to amoxicillin-clavunate, ceftriaxone, clarithromycin and linezolid. With amoxicillin-clavunate treatment, the patient recovered and her condition remained stable, although recurrence occurred after cessation of the initial treatment. While infection by *Nocardia* is rare, clinicians should be aware of its resistance to antimicrobials including amikacin and sulfamethoxazole-trimethoprim.

1. Introduction

Nocardia is an aerobic Gram-positive filamentous rod-shaped bacterium that belongs to the Actinomycetes genus found in soil, decomposing vegetation, and other organic matter, as well as in fresh and salt water [1]. *Nocardia* species usually affect immunocompromised patients; however, immunocompetent patients comprise one-third of all nocardiosis cases. The most common predisposing factors for immunocompromised nocardiosis are long-term steroid use, neoplastic disease, and human immunodeficiency virus infection (HIV) [2]. Nocardiosis can manifest as pulmonary, disseminated, and/or subcutaneous infections. The most common manifestation of this disease is pulmonary nocardiosis, due to inhalation being the primary route of bacterial exposure, occurring most frequently in immunocompromised patients. One-half of all cases of pulmonary nocardiosis are disseminated, which involve infections in areas outside of the lungs including the pericardium, mediastinum, skin, subcutaneous tissues, and the central nervous system. Approximately 20% of cases of disseminated nocardiosis present solely with extrapulmonary disease. Primary subcutaneous nocardiosis may occur in immunocompetent patients, unlike pulmonary or disseminated

nocardiosis [2]. To date, more than 50 *Nocardia* species have been recognized as clinically significant bacteria. The recent introduction of molecular methods, such as sequencing of the 16S rRNA gene, has allowed us to reclassify the *Nocardia* genus at the species level. *N. transvalensis* was first described by Pijper and Pullinger in 1927 [3], and this isolate was later characterized biochemically by Gordon et al. [4]. However, McNeil and colleagues have reported that the *N. transvalensis* isolated showed diverse antimicrobial susceptibility patterns, and biochemical testing results suggest the presence of several biotypes within the *N. transvalensis* taxon [5]. Wilson et al. have recently reported that this *N. transvalensis* complex can be classified into four distinct groups based on the examination of biochemical characteristics, molecular differences, and wall composition of the isolates: *N. transvalensis* sensu stricto, *N. asteroides* drug pattern IV, and *N. transvalensis* new taxon 1 and 2 [6]. *N. transvalensis* new taxon 1 has been recently given the new species designation of *N. blacklokiae* by Conville et al. [7]. To the best of our knowledge, our present report is the second incidence of nocardiosis resulting from infection by *N. blacklokiae*.

2. Case

A 52-year-old woman was referred to our hospital with a 1-month history of fatigue and low-grade fever. She had a past medical history of hypothyroidism and had been followed up with, demonstrating a stable condition without medication. The patient had a history of smoking 5 cigarettes per day for 10 years. She had no history of inhalation therapy, and did not receive any medicine. A physical examination performed at the time of the initial presentation revealed the following findings: height, 161 cm; weight, 51 kg; body mass index, 19.7; blood pressure, 117/78 mmHg; body temperature, 36.3 °C; heart rate, 73 beats per min; and percutaneous oxygen saturation, 97% on room air. Chest auscultation revealed normal breath sounds. Her laboratory findings were as follows: total protein, 7.0 g/dL; albumin, 3.6 g/dL; alanine aminotransferase, 13 IU/L; aspartate aminotransferase, 19 IU/L; lactate dehydrogenase, 185 IU/L; blood urea nitrogen, 14 mg/dL; creatinine, 0.59 mg/dL; C-reactive protein, 1.98 mg/dL; white blood cell count, 4800/μL with 53.2% neutrophils and 33.5% lymphocytes; red blood cell count, 3.77×10^6/μL; hemoglobin, 11.3 g/dL; hematocrit, 34.7%; platelet count, 29.2×10^4/μL; IgG, 1489 mg/dL, IgA, 312 mg/dL and IgM 190 mg/dL. Results from an interferon-γ release assay test were negative, as was a serum IgA antibody test against a glycopeptidolipid core antigen specific to the mycobacterium avium complex. Screening for HIV infection was also negative. A chest X-ray revealed multiple diffuse nodular lesions on the bilateral lung fields, which predominated in the mid-lung area. A chest computed tomography (CT) scan also revealed multiple ill-defined centrilobular nodules and some small areas of lobular consolidation accompanied by bronchial wall thickening. These abnormalities predominated in the upper left and lower right lobes of the lung (Fig. 1a–d). The patient underwent a bronchoscopy, and bronchial washing specimens were obtained from the left B[4] and B[5] regions. Initial direct Gram staining of the specimens collected revealed numerous neutrophils and thin, branching, beaded, filamentous, Gram positive bacteria, which were positive for Kinyoun staining for acid-fast bacteria. Cultures of the specimen grew *Nocardia* species. Using 16S ribosomal RNA gene sequencing, the isolate was identified as *N. blacklokiae,* and preserved as IFM 11877. The antibiotic susceptibility of the isolate was assessed by broth microdilution according to Clinical and Laboratory Standard Institute guidelines [8]. The isolate was found to be susceptible to amoxicillin-clavunate, ceftriaxone, clarithromycin, and linezolid, and resistant to sulfamethoxazole-trimethoprim and amikacin (Table 1). As a result, the patient was given amoxicillin-clavunate (500 mg/125 mg, three times a day) after which her symptoms gradually improved. Seven months after the initiation of antibiotics, a chest CT showed improvement of the multiple nodular lesions (Fig. 1e–h). Since the patient was not immunocompromised and her initial therapeutic response was good, the patient was consulted and maintenance antibiotic therapy was discontinued. The patient was carefully followed-up with, and two months after the discontinuation of antibiotic treatment she presented with recurrence of fatigue and fever.

Laboratory findings demonstrated elevated CRP levels, and a chest X-ray revealed recurrence of nodular opacities in both lung fields. The patient was diagnosed with recurring pulmonary nocardiosis and amoxicillin-clavunate was reintroduced along with clarithromycin (200mg, two times a day). Three months after the initiation of this antibiotic therapy, with which her symptoms gradually improved, clarithromycin was discontinued and maintenance monotherapy with amoxicillin-clavunate was prescribed. After twenty months of maintenance therapy, the patient was free from recurrence (Fig. 2).

3. Discussion

To the best of our knowledge, this is the second reported case of nocardiosis caused by *N. blacklokiae*. The recent introduction of molecular techniques, such as sequencing of the 16S rRNA genes, allows for better identification, and therefore more accurate taxonomic classification, of *Nocardia* spp. The new taxon *N. blacklokiae*, formerly classified as *N. transvalensis*, was first described in 2008 by Conville et al., who identified four strains of *N. blacklokiae* [7]. They also described one detailed clinical case of pulmonary nocardiosis caused by *N. blacklokiae* in an immunocompromised host with chronic alcoholism. Although nocardiosis caused by this species seems to be extremely rare, the case reported here and that reported by Conville et al. highlight the pathogenicity of *N. blacklokiae*. Immunocompromised hosts are frequently infected by *Nocardia* spp., comprising two thirds of all nocardiosis cases, however immunocompetent hosts may also be susceptible to infection [9]. In the case reported here, the patient was immunocompetent; she did not take any immunosuppressants and had no comorbidities, including HIV, chronic alcoholism, diabetes mellitus. Additionally, this patient did not suffer from any known underlying pulmonary disease, such as chronic obstructive pulmonary disease, asthma, chronic sarcoidosis, or bronchiectasis. The lung is most susceptible to infection due to inhalation being the primary route of bacterial exposure, and although there have been reports of only two cases of nocardiosis caused by *N. blacklokiae*, both were of pulmonary nocardiosis. Extrapulmonary nocardiosis, which is relatively common, occurs through hematogenous dissemination or a contiguous spread of necrotizing pneumonitis with the central nervous system (CNS) being the most common site of infection. Meanwhile, primary cutaneous and soft tissue nocardiosis can result from traumatic injury to the skin that involves contamination with soil. Some *Nocardia* species have a tendency to affect peculiar organ, as is the case with *N. brasiliensis,* which often affects the skin [1]. Cumulative future case reports and studies are needed to elucidate the clinical features of nocardiosis caused by *N. blacklokiae*.

Traditionally, sulfamethoxazole-trimethoprim has been considered the first line of drug treatment of nocardiosis. Several recent reports have suggested that linezolid may be a promising alternative oral agent for patients with nocardiosis who cannot receive sulfamethoxazole-trimethoprim because of intolerance or resistance [2,10]. However, there are potential disadvantages to prescribing this antimicrobial as a
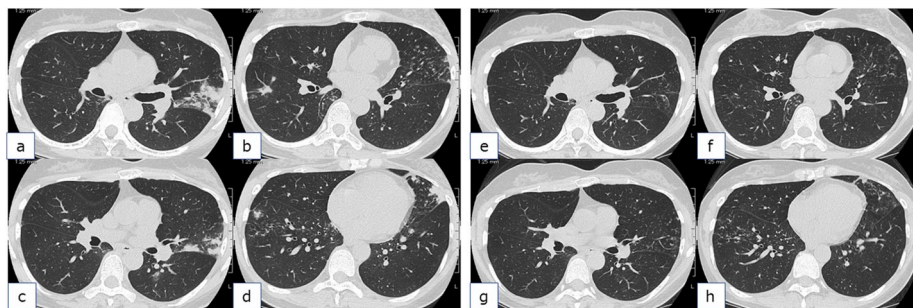

Fig. 1. Chest computed tomography (CT) at the first visit revealed multiple ill-defined centrilobular nodules and small areas of lobular consolidation predominating in the left upper lobe and right lower lobe (a–d). Chest CT performed 7 months after the initiation of the antibiotic therapy with amoxicillin-clavunate revealed improvement of the abnormalities.

Table 1
Published cases of nocardiosis caused by N.blacklokiae.

Author	year	symptom	infected organ	Comorbidities	AMPC/CVA	CTX	CTRX	CPFX	IMPM	MINO	AMK	SMX/TMP	LZD	CAM	Antibiotics	outcome
Conville	2008	fever, chest pain, and cough with purulent sputum production	lung	chronic alcholism	32/16 (R)	2 (S)	2 (S)	8 (R)	0.5 (S)	>16 (R)	>16 (R)	76/4 (R)	NA	NA	sulfadiazine, sulfadimidine, SMX/TMP, amoxicillin, amikacin	survived
This case	2019	low grade fever and fatigue	lung	immunocompetent	2/1 (S)	4 (S)	4 (S)	2 (I)	8 (I)	2 (I)	16 (R)	152/8 (R)	4 (S)	<0.25 (S)	AMPC/CVA and CAM	survived

AMPC/CVA: amoxicillin-clavunate, AMK: amikacin, CAM: clarithromycin, CPFX: ciprofloxacin, CTX: cefotaxime, CTRX: ceftriaxone, IMPM: imipenem, LZD: linezolid, MINO: minocycline, SMX/TMP: sulfamethoxazole-trimethoprim.

long-term therapy, including both cost and adverse side effects such as thrombocytopenia and anemia [10]. For seriously ill patients who cannot be treated with oral agents, or those infected with isolates resistant to sulfamethoxazole-trimethoprim, parental imipenem, ceftriaxone, cefotaxime, or amikacin may be used instead [11]. As for oral agents, minocycline is well tolerated and can be used for nocardiosis in less seriously ill patients [11]. If in vitro activity is shown, amoxicillin-clavunate, doxycycline, erythromycin, clarithromycin, or fluoroquinolones may be used as alternative oral agents, although there is less evidence of their efficacy in treating nocardiosis [11]. In this case, as the patient was not seriously ill, we first considered treatment using oral agents. Given the isolate's resistance to sulfamethoxazole-trimethoprim and minocycline, potential oral agents that shown to be effective in vitro included linezolid, clarithromycin, and amoxicillin-clavunate. Although linezolid is more commonly used to treat nocardiosis, several reports describe amoxicillin-clavunate as an effective treatment when used in combination with other drugs [12–14], however Arduino et al. reported two cases in which nocardiosis was successfully treated with amoxicillin-clavunate alone [12]. In the case described here, the patient chose to treat with amoxicillin-clavunate first, rather than linezolid, due to the high cost and adverse outcomes of long-term linezolid therapy. All *N. blacklokiae* isolated described by Conville et al., in addition to those in the case reported here, were consistently resistant to amikacin and susceptible to linezolid [7]. Although there was no detailed description of the susceptibility testing results of the remaining strains reported by Conville et al., at least two out of five strains have been reported to be resistant to sulfamethoxazole-trimethoprim. Clinicians should be aware of this relatively high resistance rate of *N. blacklokiae* against sulfamethoxazole-trimethoprim, as well as amikacin, in the treatment of nocardiosis caused by *N. blacklokiae*. As with nocardiosis caused by other *Nocardia* species, if the patient is severely infected, combination therapy may be warranted until the species is identified and antimicrobial susceptibility testing is performed.

In this case, the patient's pulmonary lesion and respiratory symptoms had prominently resolved following amoxicillin-clavunate treatment for seven months, but relapsed after cessation of the treatment. We reintroduced amoxicillin-clavunate along with clarithromycin for three months, which immediately showed efficacy, and aim to continue amoxicillin-clavunate monotherapy for at least one year. The optimal duration of antimicrobial treatment for nocardiosis has yet to be determined, but treatment is generally prolonged to minimize the risk of disease relapse. Immunocompetent patients with pulmonary or multifocal disseminated (non-CNS) nocardiosis may be successfully treated with 6–12 months of antimicrobial therapy, while immunocompromised patients and those with CNS disease should receive at least 12 months of antimicrobial therapy with the appropriate monitoring [1].

4. Conclusion

In conclusion, to the best of our knowledge, this is the second reported case of nocardiosis caused by *N. blacklokiae*. Despite its rarity, clinicians should be aware of amikacin resistance and the relatively high resistance rate against the other antimicrobials, including sulfamethoxazole-trimethoprim. Identification of the species, coupled with antimicrobial susceptibility testing, are crucial for optimal nocardiosis disease management.

ICMJE statement

All authors meet the ICMJE authorship criteria.

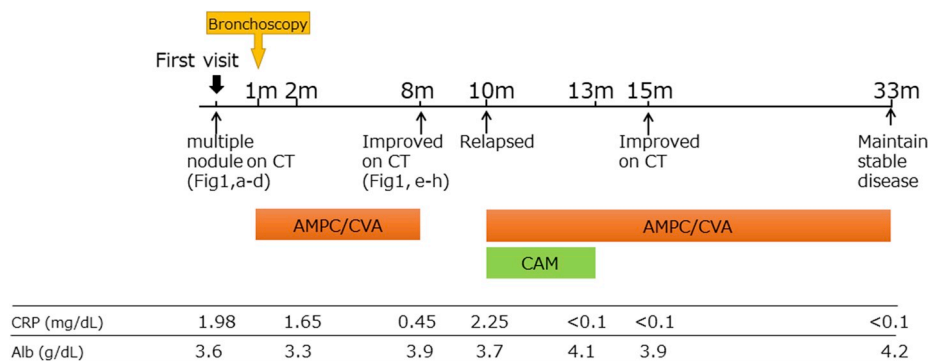**Declaration of competing interest**

None.

Fig. 2. The clinical course of treatment. Alb: albumin, AMPC/CVA: amoxicillin-clavunate, CAM: clarithromycin, CRP: C-reactive protein, CT: computed tomography, m: month(s).

Acknowledgments

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